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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,264	11/03/2003	John Byrd	18525-04052	3693

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

. Office Action Summary	Application No.	Applicant(s)	
	10/700,264	BYRD ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *13-15 and 23-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO ARGUMENTS

The Amendment filed on 8/15/06 in response to the previous Non-Final Office Action (3/30/06) is acknowledged and has been entered.

Claims 1-36 are pending. Claims 13-15 and 23-30 have been previously withdrawn for non-elected invention. Claims 1-12 and 16-22 are under consideration.

The text of those sections of Title 35, U.S.Code not included in this action can be found in the prior Office Action.

Response to Arguments

Rejection under 35 USC § 103

1. Claims 1-4, 6-7, 16-17, and 19-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Golay et al., in view of Hogan et al., Fongeca et al., Witzig et al., and Catovsky D as stated below.

> Golay et al., teach that a method of determining the susceptibility of a patient with chronic lymphocyte leukemia (CLL) to Rituximab. Golay et al., teach that the levels of CD20 expression in CLL cells determine the susceptibility to the response to Rituximab (page 3386, col 1, para 2 and figure 8). Golay et al., teach that Rituximab-mediated lysis of CLL cell depends primarily on the levels of expression of CD20 molecule on the cells (page 3386, col 1, para 1). Golay et al., also teach that Rituximab lysis of CLL cells is correlated highly significantly with number of CD20 molecules per cells and these results could be applied to analyze the role of CD20 expression in the in vivo response of different patients to rituximab (page 3388, col 2, line5-15).
>
> Golay et al., do not teach the relationship between abnormalities of chromosome and expression of CD20 and do not teach FISH and probes for detection of abnormalities of chromosome.
>
> Hogan et al., teach that all the CD20 positive CLL cells have 13q14 deletion, which is detected by FISH using probe Locus specific probes (LSI) D13S319 (Rb1 D13S319, abstract, line 7; page 78, col 2, para 1,). LSI 13 is Rb as evidenced by Fongeca et al., (Leukemia, vol 15, page 981-6, 2001).
>
> Witzig et al., teach that the CD20 positive CLL cells have Trisomy 12 detected by FISH using a probe specific for centromere of chromosome 12 (CEP 12).
>
> Catovsky D teaches that chromosome deletion 17p13.1 results in p53 deletion and dysfunction, which is associated with CLL and frequent failure to respond to therapy (page S9, col 1, para 1).
>
> It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method for predicting the response of a patient with CLL treated with an agent binding to CD20 comprising Rituximab. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the teachings of Hogan et al., Witzig et al., and Catovsky D to the teaching of Golay et al., to predict the response of a patient with specific type of CLL to a treatment with antibody to CD20 (Rituximab) after analyzing the CLL with the abnormalities of chromosome, (deletion of chromosome) because both Hogan et al., and Witzig et al., have shown that CD20 positive CLL cells have 13q14 deletion and Trisomy 12, which could be detected by FISH using probe D13S319 or probe CEP 12 and because Catovsky D has shown that deletion 17p13.1 only result in p53 deletion not others. One of ordinary skill in the art would have been motivated with a reasonable expectation

of success to predict whether a patient can respond to the treatment of Rituximab after knowing the type of chromosome deletion because Golay et al., have shown that the patient, who responds to the Rituximab treatment, has malignant leukemic CD20 positive B cells.

The response filed 8/15/06 has been carefully considered but is deemed not to be persuasive. The response states that *the cited references, alone or in combination, do not teach or suggest that the presence of 17q13.1 deletion indicates that a patient would be refractory to treatment and that the presence of 17q13.1 deletion and one or more of 13q14.3, 11q22-q23 and trisomy 12 abnormalities indicates that a patient will be responsive to treatment with a therapeutic agent that binds to CD20 on the B-lymphocytes.* In response to this argument, a method of predicting the refractory to the treatment according to the abnormalities of del(17q13.1) together with del(13q14.3), del(11q22-q23) and trisomy 12 in the claims is not elected invention filed on 1/30/06 in the response to election/restriction and has been withdrawn from consideration in previous office and will not be considered in this office action. Independent claims 1 and 16 are drawn to an invention of predicting the response of a patient with Chronic lymphocytic leukemia (CLL) to a treatment with an agent (Rituximab, antibody to CD20) binding to CD20 expressed on the leukemia B-cells, when the patient has absence of del (17p13.1) abnormality together with the presence of one or more del(13q14.3), del(11q22-q23) and trisomy 12 abnormality. One skilled in the art would understand that "the absence of del(17p13.1) abnormality "in the claims means a normal 17q13.1 or no chromosome deletion in area 17p13.1 in the leukemia patient. Thus, the claims would be interpreted as a method for predicting the response of a CLL patient with $CD20^+$ B cell leukemia to the treatment of Rituximab by determining normal 17p13.1 plus one or more of the abnormal chromosomes with del(13q14.3), del(11q22-q23) and trisomy 12 deletion and the methods has been taught and suggested by Golay et al., Hogan et al., Fongeca et al., Witzig et al., and Catovsky D in combination.

Applicants further argue that the *primary reference by Golay et al., do not concern the chromosome abnormality and not suggest that 17p13.1deletion and one or more of del(13q14.3), del(11q22-q23) and trisomy 12 abnormalities indicate the response of a patient to the treatment* and argue that *Hogan, Fonseca, and Witzig do not provide the lacking of Golay and no*

suggestion about the presence of 17q13.1 deletion. In response to this argument, as discussed above, the method objective is predicting the response to the rituximab treatment by determining the absence of deletion of 17p13.1 (normal 17p13.1) together with the presence of deletion of one or more of 13q14.3, 11q22-q23 or trisomy in the patients with $CD20^+$ B cell leukemia. First, Golay et al., teach that a patient with $CD20^+$ B-leukemia is response to rituximab treatment. Catovsky teaches that a deletion of 17p13.1 alone in CLL patients have no response to the rituximab treatment. Both references in combination indicate that the CD20 expression, not 17p13.1 deletion, in B-leukemia cell of a CLL patient is a key factor for the response to the treatment with CD20 antibody, rituximab. Furthermore, Witzig et al., and Hogan et al., teach that CLL patients with $CD20^+$B-lymphocytic leukemia cells have del(13q14.3 or deletion of trisomy, which suggest that the abnormality of these chromosomes contributes to the $CD20^+$B-lymphocytic leukemia cell development. Thus, all the reference in combination suggest that the patients responding to the rituximab treatment have normal 17q13.1 and abnormal 13q14.3 or trisomy, and abnormality of these chromosome may result in the CD20 expression in B-leukemia cells, which are bound and lysed by antibody to CD20, rituximab. Accordingly, it would be obvious for one skilled in the art to use the method to predict rituximab treatment result based on the absence of 17q13.1 deletion (normal 17q13.1) and the presence of 13q14.3 or trisomy deletion. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to use the method to in clinic to prepare the treatment plan for a CLL patient with or without CD20 expression and deletion of 17p13 after combining all of the teachings together. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained for the reason of record.

2. Claims 1-8 and 16-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Golay et al., Catovsky D, Hogan et al., and Witzig et al., further in view of Morrison and Stilgenbauer et al., as stated below.

The teachings of Golay et al., Hogan et al., Witzig et al., and Catovsky D are set forth above.

Golay et al., Hogan et al., Witzig et al., and Catovsky do not teach detecting deletion of 17p13.1 of chromosome 17 and 11q22-q23 of chromosomal 12 by FISH using the probe LSI 53 and ATM probe.

Morrison et al., teach polynucleotide probe LSI p53, which is complementary to and hybridize with target region 17p13.1 of chromosomal 17.

Stilgenbauer et al., teach ATM probe for detecting a deletion in 11q22-q23.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method for predicting the respond of a patient with CLL treated with an agent binding to CD20 comprising Rituximab. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the teachings of Hogan et al., Witzig et al., Catovsky D, Morrison et al., and Stilgenbauer et al., to the teaching of Golay et al., to predict the response of a patient with specific type of CLL to a treatment with antibody to CD20 (Rituximab) after analyzing the CLL with the abnormalities of chromosome, (deletion of chromosome) because Hogan et al., Witzig et al., and Catovsky D, have shown that different deletions of chromosome result in the abnormal expression of protein involved in B-cell malignancy comprising CLL and CD20 positive CLL cells having 13q14 deletion and Trisomy 12 detected by FISH using probe D13S319 or probe CEP 12, because Catovsky D, has shown that the chromosome deletion at 17p13.1 only results in p53 deletion, and because Morrison et al., and Stilgenbauer et al. have shown analysis of the cells with deletion of 17p13.1 and 11q22.3 detected by FISH using probe LSI p53 and ATM gene. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to predict whether a patient can respond to the treatment of Rituximab after knowing the type of chromosome deletion because Golay et al have shown that response to the Rituximab treatment in a CLL patient having malignant leukemic B cells, which express CD20 on the cells.

The response filed 8/15/06 has been carefully considered but is deemed not to be persuasive. The response outlined as above that *Golay et al., Catovsky, Hogan et al., and Witzig et al., alone or in combination do not teach or suggest every feature as recited in the independent claim 1 and 16.* The response also states that *Morrison and Stilgenbauer do not provide what Golay et al., Catovsky, Hogan et al., and Witzig lack, Stilgenbauer et al., concern using chromosome probe in mantle cell lymphoma, and neither the teaching alone nor in combination are concerned with predicting the response of a patient with CLL to the treatment.* In response to the argument, the teachings of Golay et al., Catovsky, Hogan et al., and Witzig in combination being obvious for the claimed method have been discussed above. Morrison et al., teach a method step recited in claim 5 and 18, in which 17p13.1 was in situ hybridized with fluorescence labeled probe LSI p53, and Stilgenbauser et al., teach a method step recited in claim 8 and 21, in which 11q22-q23 was in situ hybridized with fluorescence labeled probe ATM. Again, as discussed above, it would be obvious for one skilled in the art to combine the methods to predict treatment result based on the absence of del(17p13) abnormality and the presence of abnormality of the chromosomes based on the teachings in combination. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to use the methods

in clinic to prepare the treatment plan for a CLL patient with or without CD20 expression and deletion of 17p13 after combining some or all of the teachings together. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained for the reason of record.

3. Claims 9-12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Morrison et al., in view of Fonseca et al., and Stilgenbauer et aland Croce et al., as stated below.

> Morrison et al., teach polynucleotide probe LSI p53, which is complementary to and hybridize with target resin 17p13.1 of chromosomal 17 and probe CEP12, which is complementary to and hybridize with target to 12p11.1-q11 region of chromosome 12 (page 11, table 1). Morrison et al., teach a method of using the combination of probes for detecting cancer that include hybridizing a set of chromosomal probes to a biological sample obtained from a patients comprising CLL patients (abstract and entire reference).
>
> Morrison et al., do not teach probe for 11q 22.3 and 13q14.3 and a kit containing the probes.
>
> Fonseca et al., teach a probe LSI D13S319, which is complementary to and hybridize with target resin 13q14.3 of chromosomal 13.
>
> Stilgenbauer et al., teach ATM probe for detecting a deletion in 11q22-q23.
>
> Formation of a kit using known component is within the purviews of one skilled in the art. For example, Croce et al., teach diagnostic kit comprising a DNA probe as an active ingredient (col 44, line 32-67).
>
> It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make a diagnostic kit comprising the probes, LSI p53, CEP12, taught by Morrison et al., and probes, LSI D13S319, taught by Fonseca et al., and ATM probe taught by Stilgenbauer et al., for determining the chemosensitivity of CLL patient to treatment. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to combine the teachings of Morrison et al., Fonseca et al., and Stilgenbauer et al., to the teaching of Croce et al., to make a diagnostic kit containing all the DNA probes for detection of deletion in chromosomes 17p13.1, 12p11.1-q11, 11q 22.3, and 13q14.3 because Morrison et al., have shown a probe LSI p53 and CEP12 for detection of deletion of 17p13.1 of chromosomal 17 and deletion of 12p11.1-q11 of chromosomal 12, Fonseca et al., have shown a probe LSI D13S319, for detection of deletion 13q14.3 of chromosomal 13, Stilgenbauer et al., for have shown a probe ATM probe for detecting a deletion in 11q22-q23 of chromosomal 12 and Croce et al., have shown how to make a diagnostic kit comprising a DNA probe as an active ingredient.

The response filed 8/15/06 has been carefully considered but is deemed not to be persuasive. Applicants argue that *Morrison does not teach or suggest diagnostic kit for determining the chemosensitivity of a CLL patient to any type of treatment specific for CD20+ B lymphocytes and neither Fonseca, Stilgenbauer, nor Croce provides what Morrison lacks. Even if combined, the teachings do not provide <u>the method</u> recited in claim 9-12.* In response this argument, first, claims 9-12 are drawn to a diagnostic kit, which is a product claims, not a method claims. The intent use of the product would not give a weight for patentability for a product claims. Second, in this case the kit containing the same components taught by references could

be used for a detection of cytogenetic abnormality in different situations comprising the CLL patients treated with rituximab as long as the probes LSI p53 for 17p13.1, LSI D13S319 for 13q14.3, ATM probe for 11q22-q23, CEP for 12p11.1-q11 and ATM for 11q22.3 are included in the kit. Since all the probes are disclosed by the references taught by Morrison et al., Fonseca et al., Stilgenbauer et al., and Croce et al., as *stated* ***In re Kerkhoven,*** 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980), "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to form a kit with all the probes taught by the references for determining the chemosensitivity of a CLL patient in order to prepare the treatment plan or predict treatment result for the patients. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained for the reason of record.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER